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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/295,925	04/21/1999	PHALGUN B. JOSHI	16303-007510	7753

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/295,925	Applicant(s) JOSHI ET AL.	
	Examiner Joseph Woitach	Art Unit 1632	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *13-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 4, 2002, paper number 22, has been entered.

DETAILED ACTION

This application filed April 21, 1999 claims benefit to provisional applications: 60/028,665, filed April 22, 1998; 60/111,653, filed December 9, 1998; and 60/111,637, filed December 9, 1998.

Applicants have not filed claim amendments nor provided additional arguments with the instant request for the continued prosecution application 09/295,925. Therefore, all claims are drawn to the same invention claimed in the parent application prior to the filing of this continued examination under 37 CFR 1.114. Thus, the grounds of rejection set forth in the Final Office Action, paper number 15, are maintained. The basis of the final rejections are reiterated below for Applicants' convenience.

Claims 1-46 are currently pending.

Election/Restriction

Applicants' election made March 9, 2000, paper number 9, was made with traverse. Applicants argue that the Examiners summary of the previous response to the restriction requirement was incorrect. Specifically, Applicants previous amendment stated that all three groups stem from a common concept and theory and thus are related, and to exam groups I-III concurrently would not be an undue burden to the Examiner. Further, it is argued that amendments to the claims in Group I have made the invention more clear and that the inventions of Group I and Group II are similar. Applicants cite MPEP 803 for support of their arguments. Applicants arguments have been fully considered but not found persuasive.

In the restriction requirement presented in the previous office action, each of the groups are distinct inventions as restricted and amendments to the claims have not changed these groupings. Examiner presented arguments that use of the invention of Group I would not anticipate the invention of Group II and III and a search for each of these inventions would not be co-extensive. For example in the case of Groups I and II, a method of increasing the efficiency of transfection of cycling cells would not result in inhibiting growth in cancer cells, even in light of the amendment to clarify claim 1. The newly added claim 46, which is dependent on claim 1, will be examined with claims 1-12. For the reasons above and in the previous office action the restriction is found proper and made FINAL.

Claims 1-46 are pending. Claim 13-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 1-12 and 46 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 stand and claim 46 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells sensitive to the effects of electromagnetic radiation, does not reasonably provide enablement for all cells. Further, while being enabling for x-ray radiation, the specification does not reasonably provide enablement for the whole spectrum of electromagnetic radiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue that the possibility that some cells may be insensitive to radiation does not in and of itself indicate that the claims are not enabled, and that the teachings of Vogelstein *et al.* are mischaracterized. Further, it is argued that the initial burden of demonstrating that other forms of electromagnetic radiation besides X-rays can be used to synchronize cells has not been presented by the Examiner. Finally, Applicants are unclear in Examiners arguments regarding

the synchronization of cells with X-rays in any other portion of the cell cycle besides G2/M. (applicants amendment pages 3-7). Applicants arguments have been fully considered but not found persuasive.

As discussed in the previous office action it is known in the art that chemical compounds which disrupt essential elements which affect cell cycle control and electromagnetic radiation that alter the DNA of a cell, such as x-ray and γ-ray radiation, will cause the cell to stop cycling at specific cell cycle check points until either the chemical is removed or the damaged DNA is repaired. Further, the specification demonstrate that cell cycle synchronization by chemical means can increase the efficiency of transformation and then by association the conclusion is made that x-rays increase the efficiency for similar reasons, i.e. cell cycle synchronization. Examiner agrees in part with some of Applicants arguments. First, the arguments and newly supplied art (Bolognia *et al.* and Rubin *et al.*) do demonstrate that cells can be synchronized through the use of high energy electromagnetic radiation such as X-rays and gamma rays, however one of skill in art would not know how to practice the invention with low energy radiation, in particular forms of radiation which do not penetrate the cell. It is well known in the art that high energy radiation can penetrate far into a cell or a subject *in vivo*, and through the mechanisms of DNA damage repair the cells become synchronized during the repair process, particularly at the G2/M stage of the cell cycle. Without asserting a specific mechanism for synchronization of a cell with high energy radiation, one of ordinary skill in the art would not know how to achieve synchronization with low energy radiation. In particular, where the well

known physical limitations and ability of low energy radiation to affect cells within a subject are not clearly demonstrated in the specification. Neither guidance nor examples are provided demonstrating how one of ordinary skill in the art would use non-penetrating low energy radiation.

Further, there is no guidance nor examples which demonstrate that the cell can be synchronized with high energy radiation in any other state than G2/M, and so in claims 3, 4 and 5, it is unclear how a source of electromagnetic radiation can synchronize the cell at different points in the cell cycle. Applicants claims encompass synchronization at any point in the cell cycle. While other parts of the cell cycle can be attained after the cells have been synchronized and re-enter the cell cycle, the specification fails to teach how to synchronize cells in parts of the cell cycle other than G2/M. In the instant case the mechanism of synchronization is important, because it is well accepted in the art that ionizing radiation synchronizes the cell by virtue of DNA damage and damage repair mechanisms of the cell. The instant specification fails to provide the necessary guidance or demonstrate by example that cells can be synchronized at nay other points in the cell cycle by electromagnetic radiation other than G2/M.. The instant specification and the art of record fails to provide the nexus between synchronizing cells at G2/M with high energy radiation and the ability to synchronize the cell at other parts of the cell cycle with the same radiation or any other form of radiation encompassed by the claims.

With respect to applicants arguments regarding cells resistant to electromagnetic radiation and the use of Vogelstein *et al.*, it is first noted that applicants claims as written encompass

synchronization of any cell type *in vitro* and *in vivo*. As stated in the previous office action while it has been established in the art that cells can be sensitive to certain types of electromagnetic radiation, there are many transformed cells which have acquired genetic alterations which make them insensitive to the effects of radiation and other cell synchronizing agents. Vogelstein *et al.* is used as an example of one such cell type, p21-deficient cells which are defective in cell cycle check-point control and can not be synchronized by common agents, including radiation (figure 2c, figures 3i and 3k). While applicants assertion is true that these cells can be synchronized by chemical agents, they can not however be synchronized by X-ray radiation. The instant claims encompass transformed cells many of which are known in the art to be resistant and would not be altered by radiation. Further since they are not affected by radiation, the efficiency of transfection would not be affected by the method recited in the claims. Thus the method is limited to cells which are sensitive to electromagnetic radiation. In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill in the art to practice the full scope of the invention as claimed. Therefore for the reasons above and of record, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Applicants amendments to the claims have obviated these rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11 and 12 stand and claim 46 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* in view of Spang-Thomsen *et al.*

Applicants argue that a *prima facie* case for obviousness has not been made and that a reasonable expectation of successes has not been demonstrated. Specifically, applicants argue that Yorifuji *et al.* teach that synchronization of cells *in vitro* increase the efficiency of

transfection not *in vivo* (applicants amendment pages 8-9). Secondly, it is argued that Spang-Thomsen *et al.* fails to provide a reasonable expectation of success because only a partial synchronization of cells was obtained by their methodology (applicants amendment pages 9-10). Applicants arguments have been fully considered but not found persuasive.

Examiner agrees with applicants summary of the references experimental results, however disagrees with the assessment of the expectation of success. First, Yorifuji *et al.* are specifically interested in the stable transformation of synchronized cells and many of their comments on gene transfer deal with this stable transformation (as noted by applicants in the title of Yorifuji reference). Regardless, Yorifuji *et al.* do demonstrate that through the use of chemicals and electromagnetic radiation that synchronized cells are more efficiently transformed at different parts of the cell cycle. As correctly summarized by applicants amendment, Spang-Thomsen *et al.* teach the synchronization of *in vivo* analyzing various conditions for the optimization of synchronizing conditions. The motivation for Spang-Thomsen *et al.* experiments is for use in combination with administration of cell cycle specific compounds, in particular for treatment of tumors (page 853; first paragraph). While applicant is also correct in asserting that only a small fraction of the cells were synchronized, this is only at days 1.5-2 (page 852; beginning of same paragraph), not the entire time course of experiments such as days 6-7 where a greater proportion of cells were synchronizes, especially at higher doses (page 853; second paragraph). Therefore, Spang-Thomsen *et al.* teach that cells can be synchronized with different amounts of x-ray radiation (page 852; figure 2 and summarized in discussion).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to synchronize the cells as taught by Spang-Thomsen *et al.* in order to increase the efficiency of stable gene transfer as observed by Yorifuji *et al.* One having ordinary skill in the art would have been motivated to use electromagnetic radiation in order to avoid the need or complicating effects of chemicals to simplify the method of synchronization *in vitro* and *in vivo*. There would have been a reasonable expectation of success given the results of Yorifuji *et al.* that different methods of synchronization were effective in increasing the transformation efficiency and thus cell cycle dependent suggesting that any form of synchronization would be effective including the x-ray radiation taught by Spang-Thomsen *et al.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Therefore, for the reasons above and of record the rejection is maintained.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* in view of Spang-Thomsen *et al.* as applied to claims 1-9, 11,12 and 46 above, and further in view of Son *et al.*

Applicants argue that the claims are not obvious over Yorifuji *et al.* in view of Spang-Thomsen *et al.* as discussed *supra*, and that Son *et al.* fails to remedy Yorifuji *et al.* in view of Spang-Thomsen *et al.* Further, that dependent claim 10 is unobvious in light of these arguments. Applicants arguments have been fully considered but not found persuasive.

First, as a formal matter, Applicants are correct in noting the Examiners error of inconsistency of citing Lechardeur *et al.* instead of Son *et al.* within the rejection. With regards to the specific rejection, as discussed above there was a reasonable expectation of success given the teachings of Yorifuji *et al.* in view of Spang-Thomsen *et al.* and it has been maintained that claims 1-9, 11, 12 and 46 are obvious over Yorifuji *et al.* in view of Spang-Thomsen *et al.* While different forms of cell transfection were well known in the art at the time of filing, Son *et al.* was to demonstrate this fact and teach specifically how to transform a cell with lipid-nucleic acid particle. Applicants do not refute the teaching of Son *et al.* Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to transform the synchronized cells as taught by Spang-Yorifuji *et al.* in view of Thomsen *et al.* with the method taught in Son *et al.* One having ordinary skill in the art would have been motivated to use lipid-nucleic acid particles to simplify the method of transfection and to make it applicable to cells which may be sensitive to transformation by electroporation. There would have been a reasonable expectation of success given the results of Son *et al.* that the method of transformation which uses the lipid-nucleic acid particle could be used for synchronized cell cultures.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Therefore, for the reasons above and of record the rejection is maintained.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Patsy Zimmerman whose telephone number is (703)308-8338.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1632